Claims

1. A pharmaceutical composition comprising (i) one or more genetically engineered microorganisms, said microorganisms comprising a nucleic acid encoding a protein that breaks down interstitial matrix or targets tumor vasculature; and (ii) a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein said nucleic acid encodes a protein selected from the group consisting of a matrix degrading protein, matrix metalloproteinases (MMPs), a protein that increases MMP production, a protein that increases collagen turnover, a protein that decreases collagen formation, a protein that increases extracellular matrix (ECM) turnover, a protein that decreases ECM formation, relaxin, collagenase, anti-fibrotic proteins, halofuginone, hyaluronidase, chondroitinase, heparatinase, and a cathepsin enzyme.

3. The pharmaceutical composition of claim 1, wherein said microorganism is a virus or a bacterium.

4. The pharmaceutical composition of claim 3, wherein said virus is selected from the group consisting of a replication defective virus, a replication selective virus, a replication competent virus, and an oncolytic virus.

5. The pharmaceutical composition of claim 4, wherein said virus is a member of a virus family selected from the group consisting of: herpesviruses, adenoviruses, adeno-associated viruses, lentiviruses, parvoviruses, papovaviruses, poxviruses, hepadnaviruses, alphaviruses, iridoviruses, alphaviruses, and retroviruses.

6. The pharmaceutical composition of claim 5, wherein said virus is a herpes simplex virus-1 comprising a mutation in a ribonucleotide reductase gene, wherein said mutation results in inactivation of said ribonucleotide reductase gene.

7. The pharmaceutical composition of claim 5, wherein said virus is an adenovirus comprising a mutation in the E1A CR-2 gene, wherein said mutation results in inactivation of said E1A CR-2 gene.

8. The pharmaceutical composition of claim 3, wherein said bacteria are selected from the group consisting of: *Salmonella bacteriophage, S. bongori, S. choleraesuis, S. enterica, S. enteritidis, S. paratyphi, S. typhi, S. typhimurium, S. typhimurium bacteriophage, Shigella boydii, S. dysenteriae, S. flexneri, S. sonnei, Staphylococcus arlettae, S. aureus, S. auricularis, S. bacteriophage, S. capitis, S. caprae, S. carnosus, S. caseolyticus, S. chromogenes, S. cohnii, S. delphini, S. epidermidis, S. equorum, S. felis, S. fleurettii, S. gallinarum, S. haemolyticus, S. hominis, S. hyicus, S. intermedius, S. kloosii, S. lentus, S. lugdunensis, S. lutrae, S. muscae, S. mutans, S. pasteuri, S. phage, S. piscifermentans, S. pulvereri, S. saccharolyticus, S. saprophyticus, S. schleiferi, S. sciuri, S. simulans, S. succinus, S. vitulinus, S. warneri, S. xylosus, Yersinia aldovae, Y. bercovieri, Y. enterocolitica, Y. frederiksenii, Y. intermedia, Y. kristensenii, Y. mollaretii, Y. pestis, Y. philomiragia, Y. pseudotuberculosis, Y. rohdei,* and *Y. ruckeri, Bifidobacterium adolescentis, B. animalis, B. bifidum, B. boum, B breve, B. coryneforme, B. dentlum, B. indicum, B. infantis, B. longum, B. magnum, B. pseudolongum, Lactobacillus bifidus, L. delbrueckil, Clostridium absonum, C. acetobutylicum, C. beijerinckii, C. bifermentans, C. butyricum, C. difficile, C. histolyticum, C. novyi, C. oncolyticum, C. pectinovorum, C. perfringens, C. sordelli, C. tetani, C. tyrobutyricum, and Corynebacterium parvum,*

9. A kit comprising (i) one or more genetically engineered microorganisms, said microorganisms comprising a nucleic acid encoding a protein that breaks down the interstitial matrix or targets the tumor vasculature, and (ii) instructions for their use for treating a cancer in a mammal.

10. The kit of claim 9, wherein said nucleic acid encodes a protein selected from the group consisting of a matrix degrading protein, matrix metalloproteinases (MMPs), a protein that increases MMP production, a protein that increases collagen turnover, a protein that decreases collagen formation, a protein that increases extracellular matrix (ECM) turnover, a protein that decreases ECM formation, relaxin, collagenase, anti-fibrotic proteins, halofuginone, hyaluronidase, chondroitinase, heparatinase, and a cathepsin enzyme.

11. The kit of claim 9, wherein said microorganism is a virus or a bacterium.

12. The kit of claim 11, wherein said virus is selected from the group consisting of a replication defective virus, a replication selective virus, a replication competent virus, and an oncolytic virus.

13. The kit of claim 12, wherein said said virus is a member of a virus family selected from the group consisting of: herpesviruses, adenoviruses, adeno-associated viruses, lentiviruses, parvoviruses, papovaviruses, poxviruses, hepadnaviruses, alphaviruses, iridoviruses, and retroviruses.

14. The kit of claim 13, wherein said virus is a herpes simplex virus-1 comprising a mutation in a ribonucleotide reductase gene, wherein said mutation results in inactivation of said ribonucleotide reductase gene.

15. The kit of claim 13, wherein said virus is an adenovirus comprising a mutation in the E1A CR-2 gene, wherein said mutation results in inactivation of said E1A CR-2 gene.

16. The kit of claim 9, wherein said bacterium is selected from the group consisting of: *Salmonella bacteriophage, S. bongori, S. choleraesuis, S. enterica, S. enteritidis, S. paratyphi, S. typhi, S. typhimurium, S. typhimurium bacteriophage, Shigella boydii, S. dysenteriae, S. flexneri, S. sonnei, Staphylococcus arlettae, S. aureus, S. auricularis, S. bacteriophage, S. capitis, S. caprae, S. carnosus, S. caseolyticus, S. chromogenes, S. cohnii, S. delphini, S. epidermidis, S. equorum, S. felis, S. fleurettii, S. gallinarum, S. haemolyticus, S. hominis, S. hyicus, S. intermedius, S. kloosii, S. lentus, S. lugdunensis, S. lutrae, S. muscae, S. mutans, S. pasteuri, S. phage, S. piscifermentans, S. pulvereri, S. saccharolyticus, S. saprophyticus, S. schleiferi, S. sciuri, S. simulans, S. succinus, S. vitulinus, S. warneri, S. xylosus, Yersinia aldovae, Y. bercovieri, Y. enterocolitica, Y. frederiksenii, Y. intermedia, Y. kristensenii, Y. mollaretii, Y. pestis, Y. philomiragia, Y. pseudotuberculosis, Y. rohdei*, and *Y. ruckeri, Bifidobacterium adolescentis, B. animalis, B. bifidum, B. boum, B breve, B. coryneforme, B. dentlum, B. indicum, B. infantis, B. longum, B. magnum, B. pseudolongum, Lactobacillus bifidus, L. delbrueckil, Clostridium absonum, C. acetobutylicum, C. beijerinckii, C. bifermentans, C. butyricum, C. difficile, C. histolyticum, C. novyi, C. oncolyticum, C. pectinovorum, C. perfringens, C. sordelli, C. tetani, C. tyrobutyricum, and Corynebacterium parvum.*

17. A method of treating a cancer in a mammal, said method comprising administering to said mammal one or more genetically engineered microorganisms, said microorganism comprising a nucleic acid encoding a protein that breaks down the interstitial matrix or targets the tumor vasculature, wherein said administering is for a time and in an amount sufficient to destroy, slow, or arrest said cancer.

18. The method of claim 17, wherein said nucleic acid encodes a protein selected from the group consisting of a matrix degrading protein, matrix metalloproteinases (MMPs), a protein that increases MMP production, a protein that increases collagen turnover, a protein that decreases collagen formation, a protein that increases extracellular matrix (ECM) turnover, a protein that decreases ECM formation, relaxin, collagenase, anti-fibrotic proteins, halofuginone, hyaluronidase, chondroitinase, heparatinase, and a cathepsin enzyme.

19. The method of claim 17, wherein said microorganism is a virus or a bacterium.

20. The method of claim 19, wherein said virus is selected from the group consisting of a replication defective virus, a replication selective virus, a replication competent virus, and an oncolytic virus.

21. The method of claim 20, wherein said said virus is a member of a virus family selected from the group consisting of: herpesviruses, adenoviruses, adeno-associated viruses, lentiviruses, parvoviruses, papovaviruses, poxviruses, hepadnaviruses, alphaviruses, iridoviruses, and retroviruses.

22. The method of claim 21, wherein said virus is a herpes simplex virus-1 comprising a mutation in a ribonucleotide reductase gene, wherein said mutation results in inactivation of said ribonucleotide reductase gene.

23. The method of claim 21, wherein said virus is an adenovirus comprising a mutation in the E1A CR-2 gene, wherein said mutation results in inactivation of said E1A CR-2 gene.

24. The method of claim 19, wherein said bacterium is selected from the group consisting of: *Salmonella bacteriophage, S. bongori, S. choleraesuis, S. enterica, S. enteritidis, S. paratyphi, S. typhi, S. typhimurium, S. typhimurium bacteriophage, Shigella boydii, S. dysenteriae, S. flexneri, S. sonnei, Staphylococcus arlettae, S. aureus, S. auricularis, S. bacteriophage, S. capitis, S. caprae, S. carnosus, S. caseolyticus, S. chromogenes, S. cohnii, S. delphini, S. epidermidis, S. equorum, S. felis, S. fleurettii, S. gallinarum, S. haemolyticus, S. hominis, S. hyicus, S. intermedius, S. kloosii, S. lentus, S. lugdunensis, S. lutrae, S. muscae, S. mutans, S. pasteuri, S. phage, S. piscifermentans, S. pulvereri, S. saccharolyticus, S. saprophyticus, S. schleiferi, S. sciuri, S. simulans, S. succinus, S. vitulinus, S. warneri, S. xylosus, Yersinia aldovae, Y. bercovieri, Y. enterocolitica, Y. frederiksenii, Y. intermedia, Y. kristensenii, Y. mollaretii, Y. pestis, Y. philomiragia, Y. pseudotuberculosis, Y. rohdei,* and *Y. ruckeri, Bifidobacterium adolescentis, B. animalis, B. bifidum, B. boum, B breve, B. coryneforme, B. dentlum, B. indicum, B. infantis, B. longum, B. magnum, B. pseudolongum, Lactobacillus bifidus, L. delbrueckil, Clostridium absonum, C. acetobutylicum, C. beijerinckii, C. bifermentans, C. butyricum, C. difficile, C. histolyticum, C. novyi, C. oncolyticum, C. pectinovorum, C. perfringens, C. sordelli, C. tetani, C. tyrobutyricum, and Corynebacterium parvum.*

25. The method of claim 17, furthering comprising administering a therapy selected from the group consisting of a chemotherapeutic agent, radiation therapy, an anti-angiogenic compound, an anti-vascular agent, an oncolytic virus.

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26. The method of claim 17, wherein said mammal is a human.